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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,156	11/03/2003	Nathan Andrew Shapira	UF-389	3799

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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

EXAMINER	
KIM, JENNIFER M	
ART UNIT	**PAPER NUMBER**
1617	

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07/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/700,156	SHAPIRA ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/13/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed April 16, 2007 have been received and entered into the application.

Applicants' election of species of atomoxetine **without** traverse is acknowledged. Accordingly, claims 1-30 have been examined only to the extent of applicants' elected species.

Specification

The abstract of the disclosure is objected to because it appears that "bupropion" is misspelled as "buproprion". Correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 1-30 are objected to because of the following informalities: It appears that "bupropion" is misspelled as "buproprion". Appropriate correction is required.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-7, 13, 14,17, 18, 20 and 25-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treatment of cognitive dysfunction", does not reasonably provide enablement for the "**prevention** of cognitive dysfunction". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method for the treatment, prevention or amelioration of medication-induced or perioperative cognitive dysfunction comprising the administration of medications or compositions comprising atomoxetine (a selective norepinephrine reuptake inhibitor) to an individual. The nature of the invention is extremely complex in that it encompasses the actual prevention of cognitive dysfunction disorder such that the subject treated with above compounds does not contract cognitive dysfunction.

Breath of the Claims: The complex of nature of the claims

greatly exacerbated by breath of the claims. The claims encompass prevention of medication-induced or perioperative cognitive dysfunction in humans which has potentially many different causes (i.e. many different mutations of medication or combination of mutations of medications; metabolites, prodrugs, surgical procedure, complications, combination of procedures, patient medical history, concomitant therapy). Each of which may or may not be addressed by the administration of the claimed compound.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds to a subject in order to actually prevent medication-induced cognitive dysfunction is minimal. All of the guidance provided by the specification is directed towards treatment rather than prevention of medication-induced cognitive dysfunction.

Working Examples: All of the working examples provided by the specification are directed toward the treatment rather than prevention of medication-induced or perioperative cognitive dysfunction.

State of the Art: While the state of the art is relatively high with regard to treatment of cognitive dysfunction, the state of the art with regard to **prevention** of such disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to prevent development of medication-induced or perioperative cognitive dysfunction.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual **prevention** of medication-induced or perioperative cognitive dysfunction in human subject with the claimed compounds makes practicing the claimed invention unpredictable in terms of prevention of medication-induced or perioperative cognitive dysfunction.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for prevention of medication-induced or perioperative cognitive dysfunction. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard to **prevention** of medication-induced or perioperative cognitive dysfunction with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding **prevention** of medication-induced or perioperative cognitive dysfunction with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it

would require undue, unpredictable experimentation to practice the claimed invention to prevent the development of medication-induced or perioperative cognitive dysfunction in a subject by administration of one of the claimed compounds.

Therefore, a method for the treatment, prevention or amelioration of medication-induced or perioperative cognitive dysfunction comprising the administration of medications or compositions comprising atomoxetine (a selective norepinephrine reuptake inhibitor) to an individual is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 10, 17 and 25 are rejected under 35 U.S.C. 102(a) as being anticipated by Michelson et al. (2003).

Michelson et al. teach that atomoxetine is effective for treatment of attention-deficit/hyperactivity disorder (ADHD). (abstract, conclusion). Michelson et al. teach that ADHD is a psychiatric disorder characterized by difficulties sustaining attention and

difficulties with impulse control. (first sentence under Introduction). Michelson et al. teach that atomoxetine was administered 60mg of daily dosage and increased to 90 mg/day and to 120mg/day.

It is noted that in the instant specification on page 6, lines 10-15, that cognitive dysfunction is defined as a condition of having **difficulty with attention**. Therefore, the teaching of Michelson et al. that atomoxetine provided an efficacious treatment of ADHD characterized by difficulties sustaining attention clearly anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3, 13,16, 18, 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michelson et al. (2003) of record.

Michelson et al. teach that atomoxetine is effective for treatment of attention-deficit/hyperactivity disorder (ADHD) (cognitive dysfunction). (abstract under conclusion). Michelson et al. teach that ADHD is a psychiatric disorder characterized by difficulties sustaining attention and difficulties with impulse control. (first sentence under Introduction). Michelson et al. teach that atomoxetine was administered 60mg of daily dosage and increased to 90 mg/day and to 120mg/day. Michelson et al. teach that bupropion, an antidepressant, is a current therapy involving treatment of ADHD.

Michelson et al. do not teach the atomoxetine in a combination with bupropion for the treatment of ADHD.

It would have been obvious to one of ordinary skill in the art to modify the teaching of Michelson et al. and incorporate bupropion in the treatment of ADHD because Michelson et al. teaches that bupropion is current therapy for treatment of ADHD. One of ordinary skill in the art would have been motivated to combine bupropion with atomoxetine to treat ADHD in order to achieve an expected additive

effect of treating ADHD. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)).

Claims 4-9, 11, 12, 14,15,19-22 and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bymaster et al. (2002) in view of Swaguchi et al. (1991) and Branconnier (1983).

Bymaster et al. teach that atomoxetine increases catecholamine in prefrontal cortex (PFC), a region involved in attention and memory in ADHD. Bymaster et al. teach that atomoxetine increase dopamine concentration in PFC 3-fold, but does not alter dopamine in stratum. This is in contrast to methylphenidate increasing catecholamine in PFC, suggesting it would not have drug abuse liabilities. (abstract).

Bymaster et al. do not teach the treatment of perioperative cognitive dysfunction set forth in claims 4 and 5 and the situations associated with cognitive dysfunction set forth in claim 8 and 11 and the employment of bupropion.

Swaguchi et al. teach that the prefrontal cortex is involved in the cognitive process of working memory. (abstract). Swaguchi et al. teach that the activation of dopamine receptors is critical for the memory processes mediated by the primate PFC. (page 949, last paragraph).

Branconnier teaches that bupropion improves cognition. (abstract).

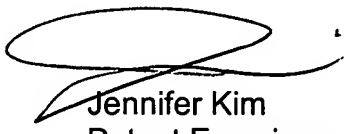
It would have been obvious to one of ordinary skill in the art to employ atomoxetine for the treatment of cognitive dysfunction because atomoxetine increases

dopamine concentration in PFC as taught by Bymaster et al. and this increase of dopamine concentration is critical for the memory process in primates as taught by Swaguchi et al. One would have been motivated to employ atomoxeine for the treatment of cognitive dysfunction in order to achieve an expected benefit of increase in attention and memory in a patient by increasing critical catecholamine concentration in PFC. It would have been obvious to one of ordinary skill in the art to employ atomoxeine for increasing cognitive process regardless of the cause such as preoperative conditions or the situation where the extensive concentration is desired because the mechanism of action involving atomoxetine for increasing dopamine concentration that is critical for the memory process is well known by Bymaster. Therefore, this mechanism of action would obviously take place in an individual upon administration regard less of causes or surrounding situations of the individual. Further, it would have been obvious to one of ordinary skill in the art to combine bupropion for the treatment of cognitive dysfunction because bupropion improves cognition as taught by Branconnier. One would have been motivated to combine bupropion with atomoxetine in order to achieve at least an additive effect in improving cognitive dysfunction. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)). Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Jennifer Kim
Patent Examiner
Art Unit 1617

Jmk
June 25, 2007